

CASE REPORT

APOCRINE CARCINOMA OF THE BREAST. CLINICAL, HISTOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES

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Received 12 Aug 2020, Accepted 20 Sept 2020

<https://doi.org/10.31688/ABMU.2020.55.4.21>

ABSTRACT

Introduction. Invasive apocrine carcinoma of the breast is a rare special subtype of mammary carcinoma and accounts for 0.3-1% of all breast malignancies. It has specific histological, immunohistochemical, and molecular genetic characteristics. The tumour cells have a unique immunohistochemical profile, which is to show Gross Cystic Disease Fluid Protein 15 (GCDFP-15) and androgen receptor (AR) positivity, as well as estrogen (ER), progesterone (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) negativity.

Case presentation. We report a case of invasive apocrine carcinoma in a 55-year-old female with a lump in the right breast and no axillary lymphadenopathy. Lumpectomy and sentinel node biopsy were performed. The histological examination and the immunohistochemical profile confirmed the diagnosis of invasive apocrine carcinoma with micrometastasis in sentinel lymph node which, to our knowledge, is the first published case. Due to the involvement of one of the resection lines from high grade apocrine ductal

RÉSUMÉ

Carcinome apocrine du sein. Caractéristiques cliniques, histologiques et immunohistochimiques

Introduction. Le carcinome apocrine invasif du sein est un sous-type spécial rare de carcinome mammaire et représente 0.3-1% de toutes les tumeurs malignes du sein. Il possède des caractéristiques génétiques histologiques, immunohistochimiques et moléculaires spécifiques. Les cellules tumorales ont un profil immunohistochimique unique, qui doit montrer la positivité de protéine liquide de la maladie kystique brute 15 (GCDFP-15) et des récepteurs aux androgènes (AR), ainsi que les œstrogènes (ER), la progestérone (PR) et la négativité du récepteur 2 du facteur de croissance épidermique humain (HER2).

Présentation du cas. Nous rapportons un cas de carcinome apocrine invasif chez une femme de 55 ans avec une bosse dans le sein droit et sans lymphadénopathie axillaire. Une lumpectomie et une biopsie du ganglion sentinelle ont été effectuées. L'examen histologique et le profil immunohistochimique ont

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carcinoma in situ (DCIS), the patient underwent right modified radical mastectomy with axillary dissection. **Conclusions.** This report is a rare specific morphological type of invasive apocrine carcinoma with micrometastasis in sentinel lymph node. The unique immunohistochemical profile, the possibility of an anti-AR therapy, and the favorable prognosis separate it from basal-like triple-negative breast cancers.

Keywords: breast cancer, invasive apocrine carcinoma, pathology, immunohistochemistry.

Abbreviations:

IAC – invasive apocrine carcinoma
 GCDFP-15 – Gross Cystic Disease Fluid Protein 15
 ER – estrogen
 PR – progesterone
 HER2 – Human Epidermal Growth Factor Receptor 2
 TNBC – triple negative breast cancer
 AR – androgen
 SLN – sentinel lymph node
 DCIS – ductal carcinoma in situ
 ICH – immunohistochemistry
 H&E – hematoxylin and eosin

INTRODUCTION

Invasive apocrine carcinoma (IAC) of the breast is a rare special subtype of mammary carcinoma, as it has specific morphological, immunohistochemical, and molecular genetic characteristics. It was first documented by Krompecher in 1916¹. From all invasive types of breast cancer, IAC represents less than 1% of cases². IAC has unique morphological and immunohistochemical characteristics; it also has the tendency to show expressions of Gross Cystic Disease Fluid Protein 15 (GCDFP-15), estrogen (ER), progesterone (PR) and Human Epidermal Growth Factor Receptor 2 (HER2) negativity. These traits place most of the cases in the category of triple negative breast cancer (TNBC)^{3,4}. Between 10-30% of TNBC cases are characterized by overexpression for androgen (AR) receptor and AR pathway activation, which is typical of apocrine carcinomas^{4,5}. This feature underlies the suggested separation of IAC of the breast into the “molecular apocrine group” and facilitates receptor target endocrine therapy^{6,7}. We present a case of a woman with triple negative, AR positive IAC with micrometastasis in sentinel lymph node (SLN).

CASE PRESENTATION

A 55-year-old woman, with a medical history of rheumatoid arthritis and three years of therapy with

confirmé le diagnostic de carcinome apocrine invasif avec micrométastase dans le ganglion lymphatique sentinelle, qui est à notre connaissance le premier cas publié. En raison de l'implication de l'une des lignes de résection d'un carcinome canalaire apocrine de haut grade in situ (CCIS), le patient a subi une mastectomie radicale modifiée à droite avec dissection axillaire.

Conclusions. Ce rapport est un type morphologique spécifique rare de carcinome apocrine invasif avec micrométastase dans le ganglion sentinelle. Le profil immunohistochimique unique, la possibilité d'une thérapie anti-AR et le pronostic favorable le séparent des cancers du sein triple négatifs de type basal.

Mots-clés: cancer du sein, carcinome apocrine invasif, pathologie, immunohistochimie.

Methotrexate Ebewe 15 mg once weekly and nine months of therapy with leflunomide 20 mg once daily, presented with an abnormal finding on screening mammography of the right breast. The patient had history of mastopathic plaque and cyst (6 mm) of the left breast and no evidence of familial cancer. The physical examination revealed no palpable mass or skin changes of the breast or pain. The mammography showed a new tumour in the upper inner quadrant of the right breast, irregular in shape, with a size of 5 mm, and single microcalcifications, assumed as category 4 according to Breast Imaging-Reporting and Data System (Figure 1). Ultrasonography images of the same breast showed a rounded hypoechoic lesion with uneven outlines, about 5-6 mm in size, in the upper inner quadrant (Figure 2).

The preoperative laboratory tests showed elevated CRP (6.26 mg/dL, reference range <5 mg/dL) and fibrinogen (452 mg/dL, 200-400 mg/dL), and normal erythrocyte sedimentation rate (ESR) (17 mm/h, 0-25 mm/h). The tumour marker CA15-3 (21.37 U/mL) was in the reference range (CA15-3 <35.0 U/mL). Lumpectomy of the suspicious lesion of the right breast and sentinel node biopsy were performed. The histopathological report described an invasive tumour with a diameter of 5 mm, microscopically composed of atypical polygonal cells, with abundant granular and eosinophilic cytoplasm (periodic acid-Schiff positivity), oval centrally located nuclei



Figure 1. Mammography revealing an isodense lesion (arrow) in the upper inner quadrant of the right breast.

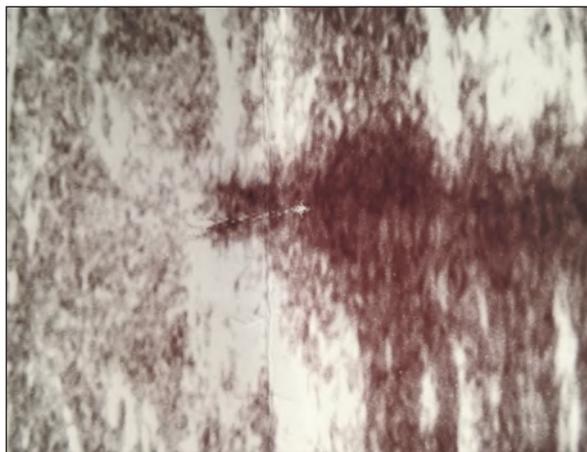


Figure 2. Ultrasonography revealing a 5 mm hypoechoic lesion in the upper inner quadrant of the right breast.

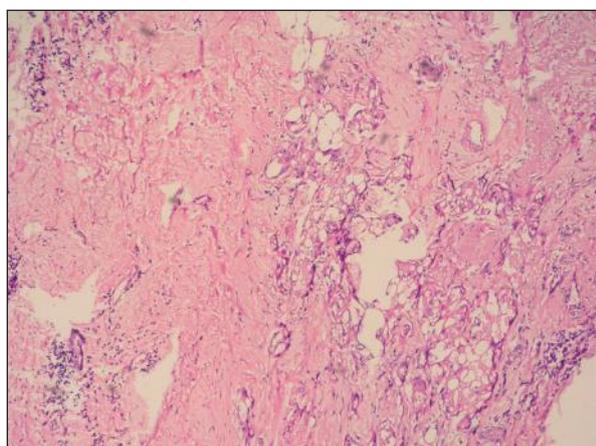


Figure 3. Histology showing invasive apocrine carcinoma of the breast – H&E, (x100).

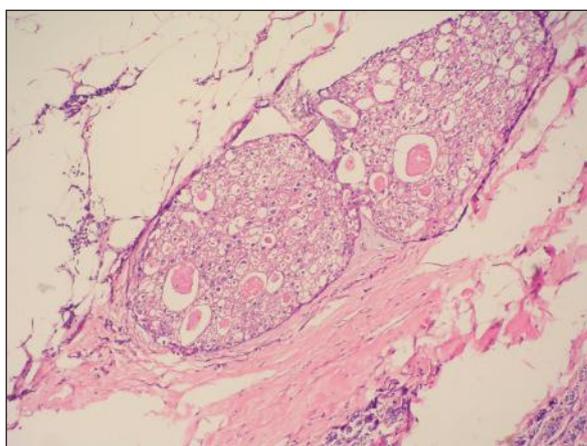


Figure 4. Apocrine ductal carcinoma in situ – H&E, (x100).

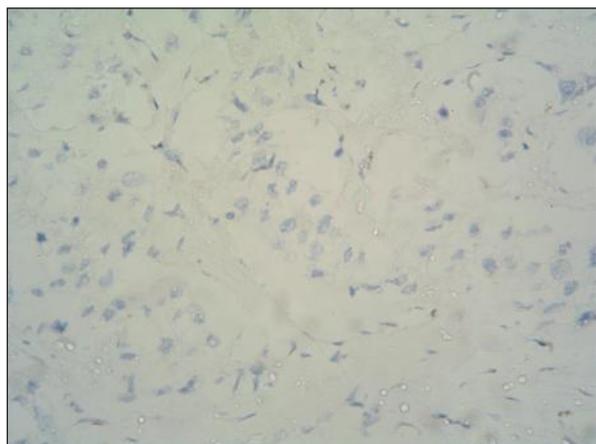


Figure 5. The apocrine tumor cells, negative for ER receptor – ICH, (x400).

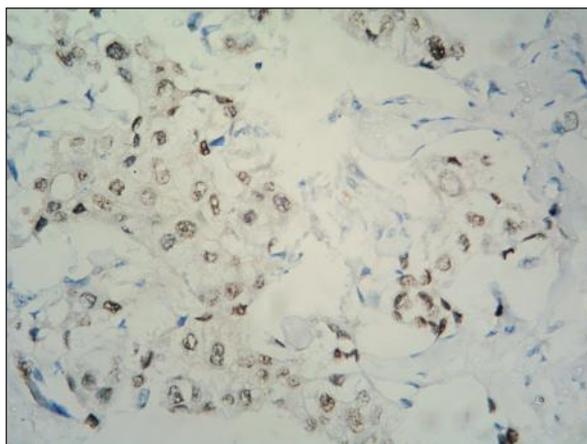


Figure 6. AR-positivity in about 80% of tumor nuclei – ICH, (x400).

with moderate pleomorphism and prominent nucleoli (Figure 3), and fields of high grade apocrine ductal carcinoma in situ (DCIS) (Figure 4). There was no lymphovascular invasion. The immunohistochemical

study of the tumour population showed a negative reaction for ER and PR receptors (Figure 5), nuclear positivity in more than 80% of tumor cells for AR receptor (Figure 6), focal immunoexpression for

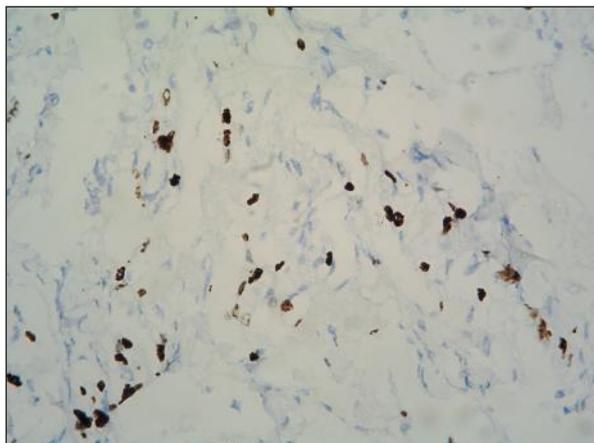


Figure 7. Ki-67 labelling index was found to be 30.1% (hot spot) – ICH, (x400).

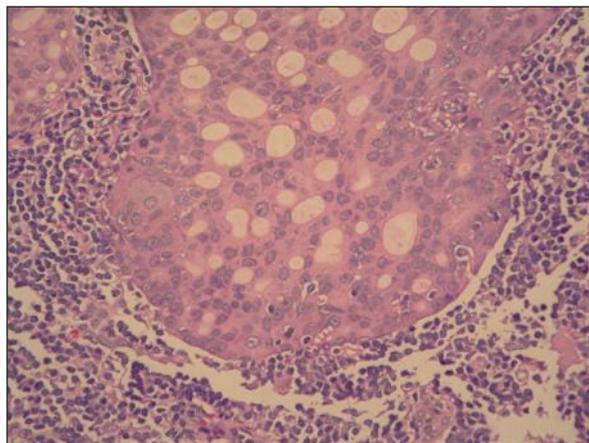


Figure 8. SLN with micrometastasis of apocrine carcinoma – H&E, (x400).

GCDFP-15, HER2 (1+) and negative reaction by chromogenic in situ hybridization method. The proliferative marker Ki-67 nuclear staining was 30.1% (Figure 7). According to the modified Bloom and Richardson scale, the histologic grading was determined as Grade 2 [score 7 (3 + 3 + 1)]. The SLN was examined in 28 steps over 60 micrometers, with a micrometastasis, the largest diameter of 1.35 mm being detected from 23rd to 27th steps (Figure 8).

Because of the involvement of one of the resection lines from high grade apocrine DCIS, a modified radical mastectomy with axillary dissection was performed. The final diagnosis was IAC-G2, pT1aSLN1micM0, St.1B/ II. By decision of the Oncology Committee, the patient was recommended adjuvant systemic chemotherapy with weekly Paclitaxel 80 mg/m² (twelve courses), hormonal anti-AR therapy with Bicalutamide accord 50 mg/daily (for 3 years), and molecular genetic analysis for BRCA1/2, which didn't detect pathogenic variants. The control examinations with positron emission tomography scan, mammography of the contralateral breast and axilla, and tumour markers over a two-year period did not show disease progression.

DISCUSSION

Malignant apocrine lesions of the breast (non-invasive and invasive) belong to the rare histological subtypes of mammary carcinomas. The incidence of IAC of the breast in the various reports varies from 0.4-15%^{1,3,5}. Gogoi et al reported the lowest incidence, 0.3-1% of breast cancers, and included them in the group of "relatively rare carcinomas"⁶. The differences in the frequency of IAC of the breast are due to differences in the morphological criteria for its determination, as well to being less often studied. The IAC

of the breast is a neoplasia composed, in 80-90%, of two types of tumour cells based on the cytoplasmic features. The first type is with abundant eosinophilic granular cytoplasm (periodic acid-Schiff +), oval nuclei and prominent nucleoli (type A cells), and the second type is with abundant foamy cytoplasm and lipid intracytoplasmic inclusions (type B cells)⁷. Tumours with less than 80% of the cells with apocrine cytological features are considered invasive ductal carcinoma with apocrine features^{7,8}. In 2005, Japaze et al standardized the criteria for IAC of the breast: 1) 75% of tumor cells have apocrine characteristics; 2) large cells with eosinophilic granular cytoplasm; 3) nucleus/cytoplasm ratio 1:2 or more; 4) large oval or pleomorphic vesicular nuclei; 5) sharp distinct cell boundaries^{3,7}. Optional (minor) criteria include: prominent nucleoli greater than 50% of the field and apical snouts into luminal spaces^{3,7}. Our case fulfilled all five criteria. Apocrine carcinomas of the breast are more common variants of invasive ductal carcinoma, while invasive lobular carcinomas are less likely to show apocrine differentiation. No clinical differences were found between IAC of the breast and invasive ductal carcinoma of no special type. They are presented as a matter of different sizes, irregular shape, without predilection and skin involvement. According to some authors, they are more often localized in the right breast, as in our case^{7,8}. There may be multifocal and/or multicentric spread and risk of developing cancer in the contralateral breast^{8,9}. IAC of the breast occurs in women between 60-70 years of age and it is extremely rare in men^{8,9}. The mean age is 57.1 years, but in the study by Kiyici et al, the mean age was 53.9 years, which is closer to the age of our patient^{5,7,10}. The IAC of the breast shows a low incidence of axillary lymph node metastases (1-4%) and lymphatic invasion compared to invasive ductal

carcinoma of no special type, which is associated with better prognosis and favorable clinical behavior^{10,11}. Isolated cases of axillary lymph node metastases have been described in the literature; however, our case is the first, to our knowledge, to be described with the presence of a micrometastasis in the SLN in a patient with rheumatoid arthritis¹². Mammography and ultrasound examinations cannot classify IAC of the breast because radiological data do not differ from invasive ductal carcinoma of no special type. Macroscopically, the tumour is yellow-brown, with a prominent cut surface, and microscopically it has invasive growth and a structure similar to invasive ductal carcinoma of no special type, but with different cytological characteristics^{13,14}. Histologically, tumour cells have eosinophilic cytoplasm, sharp borders, oval nuclei, and visible nucleoli. The IAC of the breast is graded similarly to invasive ductal carcinoma of no special type. Most of the IAC of the breast are G2-G3. According to some authors, the grading of IAC of the breast correlates with the loss of estrogen and progesterone receptors^{3,15}. The mitotic activity of neoplastic cells in the IAC of the breast is moderate or high in the context of TNBC. Regarding the differential diagnosis, IAC of the breast should be distinguished from other special types, such as oncocytic carcinoma, secretory carcinoma, lipid-cell rich carcinoma, and histiocytoid carcinoma^{3,16}. The IAC of the breast is associated with an apocrine in situ component, as observed in our case. The association with benign lesions is not well understood, but apocrine adenosis, metaplasia, and hyperplasia may have premalignant potential^{17,18}. Immunohistochemical analysis of the IAC of the breast shows that it has a unique profile, represented by negative receptor status for ER and PR, and according to Tanaka et al, these can be expressed in 16-25%^{1,17,18}. AR receptor overexpression is a hallmark of IAC of the breast, which has a predictive role for hormonal therapy, and, in the subgroup of ER-negative patients, was considered a good prognostic factor¹⁵. Other markers for apocrine differentiation are GCDFP-15, 5-alpha-reductase (expressed in 60%), gamma-glutamyl transferase, tumour-associated glycoprotein^{2,3,17}. GCDFP-15 expression in IAC of the breast correlates with small size, negative lymph nodes, and low grading, which is not confirmed by our case². HER2 in the IAC of the breast in 50% shows a negative reaction, which places it in the category of TNBCs^{4,17,18}. By molecular characteristics, the IAC of the breast belongs to the "molecular apocrine group". Studies show that apocrine tumours are different from the luminal and basal-like subtype of mammary carcinomas, because they are characterized by increased AR signals along with HER2 gene signals^{14,16,17}. In a review by Vranic

et al, the triple-negative apocrine carcinoma of the breast is subdivided into 2 apocrine groups: apocrine basal gene group and apocrine luminal gene group¹⁸. Modified radical mastectomy, chemotherapy and hormonal therapy are considered the standard treatment for patients with IAC. Information on the response to neoadjuvant chemotherapy is limited, with some studies reporting a pathological response to neoadjuvant chemotherapy in about 30-50% of apocrine carcinomas⁸. Experimental data indicate that TNBCs with AR overexpression may be sensitive to AR-antagonists (Bicalutamide) and have a complete therapeutic response^{18,19}. In the past, methotrexate has been used therapeutically as an anti-cancer drug in breast cancer, and it is also used as an immunosuppressant in the treatment of rheumatoid arthritis, in doses one-tenth or one-twentieth of the dose in the treatment of mammary carcinoma, as reported by our case. Studies show that the risk of developing breast cancer in patients with rheumatoid arthritis who are treated with methotrexate is not higher compared to that in healthy individuals²⁰.

The prognosis of patients with IAC of the breast is unknown, due to the small percentage of cases and incorrectly applied diagnostic criteria. Some authors identified better overall survival and breast cancer-specific survival for patients with AR(+) apocrine triple-negative carcinomas (over 6 years in 72%) compared with invasive ductal carcinoma of no special type (52%)^{11,19,21}.

CONCLUSIONS

Apocrine carcinoma is a rare specific morphological type of invasive breast cancer. It is a real morphological challenge that requires an immunohistochemical panel to prove its apocrine nature and distinguish it from other types of breast cancer. The unique immunohistochemical profile, the possibility of an anti-AR therapy, and the favorable prognosis separate it from the basal-like TNBCs.

Author Contributions:

T.B. and I.I. made the histopathological diagnosis. S.P. made the immunohistochemical analysis and consulted the histopathological diagnosis. S.K. – consultant of ethical issues of the article. T.B. and R.T. wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article“

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study“

„No funding for this study“

Acknowledgements:

None

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